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(54) Title: POLYPEPTIDES AND THEIR USE IN TREATMENT AND PROPHYLAXIS OF AUTO-IMMUNE DISEASE

(57) Abstract

The present invention provides polypeptide fragments of 9 or more amino acid residues which comprise the sequence VVNKIRG (SEQ ID NO:107), their use in the prevention, diagnosis and treatment of auto-immune disease such as rheumatoid arthritis and methods of preparing the fragments.

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POLYPEPTIDES AND THEIR USE IN TREATMENT AND PROPHYLAXIS OF AUTO-IMMUNE DISEASE

The present invention relates to polypeptide fragments, to their use in the prevention, diagnosis and treatment of auto-immune disease such as rheumatoid arthritis, and to methods of preparing these fragments.

Autoimmune diseases are thought to arise as a result of similarities between a foreign molecule or antigen and a molecular structure of the organism itself. Chronic forms of arthritis are thought to involve autoimmunity to constituents of the joints in particular of the connective tissues of the body.

Rheumatoid arthritis (RA) is the most common of the arthritides which exhibit autoimmune manifestations [reviewed in Elson et al, Autoimmunity (1992) 13:327]. The disease is the third most common of the elderly and causes a tremendous burden of pain and suffering. It has been known for some time that an association exists between HLA-DR4 and RA suggesting a T-cell involvement [Stasney, New Eng. J. Med. (1978) 298:869 and Watanabe et al, J. exp. Med. (1989) 169:2263] and a genetic contribution to the disease. However, recent twin studies [Silman et al, Brit. J. Rheumatol. (1993) 32:903] have suggested that the upper limit of the genetic contribution is only 15%. It follows that the main

factors contributing to the induction of RA are environmental. This contention is supported by the increased incidence of RA in South Africans as they move from villages to towns [Solomon et al, Ann, rheum. Dis. (1975) 34:128] and the increasing evidence of abnormal immune responses to microbes in patients with the disease [Deighton et al, Brit. J. Rheumatol. (1992) 31:241]. Such considerations have led to the suggestion that RA is triggered by bacterial or viral antigens which may share a high degree of homology with self protein [reviewed in reference McCulloch et al, Clin. Exp. Immunol. (1993) 92:1].

One model has proved useful in investigating environmental factors which contribute to the disease is pristane-induced arthritis (PIA). This model is based upon the finding that a proportion of mice injected intraperitoneally with the paraffin oil pristane (2, 6, 10, 14-tetramethylpentadecane) develop a chronic T-cell dependent inflammatory arthritis between 60 and 200 days later depending on the strain of mice [Potter M, J. Immunol. (1981) 127:1591, Bedwell et al, J. Immunol. (1987) 25:393, Wooley et al, Arthritis. Rheum. (1987) 32:1022, Wooley et al, Arthritis. Rheum. (1989) 32:1022 and Levitt et al, J. Rheumatol. (1992) 19:1342]. The time course of PIA thus distinguishes it from other established animal models resembling RA such as adjuvant arthritis, streptococcal cell wall arthritis and

collagen-induced arthritis. Histolopathologically arthritis is characterised by cell infiltration and synoviocyte hyperplasia with cartilage erosions and the formation of pannus [Bedwell et al, J. Immunol. (1987) 25:393, Hopkins et al, Rheumatol. Int. (1984) 5:21 and Thompson et al, Imm. Let. (1993) 36:227].

Recent work has demonstrated that the microbial environment influences the development of PIA. Specific pathogen free (SPF) mice maintained under sterile conditions in an isolator are resistant to the development of PIA whilst the return of such animals to a conventional environment restores their susceptibility to the induction of the disease [Thompson et al, Imm. Let. (1993) 36:227]. Although the resident bowel flora differs between susceptible and refractory mice [Thompson et al, Imm. Let. (1993) 36:227], it is not known if this change affects susceptibility to the disease or indeed how exposure to microbes renders mice susceptible to the development of PIA. However, it is known that serum of mice with PIA contains raised levels of antibodies to the immunodominant mycobacterial 65kD heat shock protein (hsp65) as compared with age matched normal animals or pristane injected mice which failed to develop the disease.

It has long been recognised that heat shock proteins (hsp's) are immunodominant antigens in a number of

infectious diseases, such as tuberculosis and leishmania. These infectious diseases can have similar abnormalities as observed in RA such as raised agalactosyl-IgG levels, the organs involved and range of autoantibodies present. Since environmental factors are clearly important in RA, microbial agents and hence hsp's were implicated.

Hsps are grouped in gene families according to their molecular weight and sequence homology within individual groups. For example, hsp60 (60KD) gene family includes members hsp65 (mycobacterial) and hsp58 (mammalian).

It was found that splenic T-cells from arthritic mice proliferate more vigorously *in vitro* in response to hsp65 than T-cells from age matched normal or non-arthritic mice. Furthermore, if the mice are immunised with hsp65 in incomplete Freud's adjuvant (IFA) prior to pristane challenge, the disease will not develop [Thompson et al, Eur. J. Immunol. (1990) 20:2479 and Thompson et al, Autoimmunity, (1991) 11:89]. This protective effect is specific to hsp65 and is not induced by the E.coli equivalent GroEl or other unrelated antigens [Thompson et al, Eur. J. Immunol. (1990) 20:2479] and cannot be attributed to antigenic competition [Barker et al, Autoimmunity. (1992) 14:73]. These findings raise the possibility that mice become sensitised to hsp by exposure to microbial flora in the environment and that this process is necessary for the induction of arthritis

by pristane injection. If so, it would be predicted that there is a relationship between sensitisation to hsp65 and susceptibility to PIA. Experiments carried out by the applicants suggest that this hypothesis is correct.

One possibility which would explain how PIA could develop from such sensitisation is that pristane promotes an immune response to epitopes on microbial hsp65 which cross react with self (mammalian) hsp58 [Thompson et al, Imm. Let. (1993) 36:227 and Thompson et al, Eur. J. Immunol. (1990) 20:2479]. This suggestion gains credence from the fact that hsps are dominant antigens in the immune response to microorganisms, despite their extraordinarily high sequence conservation throughout the eukaryotic and prokaryotic kingdoms [Cohen et al, Immunol. Today, (1991) 12 105]. Thus, every microbial hsp is studded with self epitopes for any animal with an immune system. Moreover, they are normal constituents of all cells although their synthesis is increased by many different forms of cellular stress. Since hsp 58 has been detected in the joints of patients with RA [Karlsson-Parra et al, Scand. J. Immunol. (1990) 31:283] and T-cells from mice with PIA react with joint extracts [Thompson et al, Eur. J. Immunol. (1990) 20:2479] it seems reasonable to postulate that hsp58 could be a target antigen in the joints of mice developing PIA. This hypothesis may explain the paradox that both mice with PIA and animals protected from the development of arthritis by hps65 preimmunisation exhibit elevated

immune responses to the 65kD mycobacterial heat shock protein. It would be expected that only mice with PIA should develop autoimmune responses to the 60kD family of hsps whereas the response of mice pre-immunised with hsp65 should be restricted to microbial specific determinants. In other words, the response elicted by immunisation with hps65 in IFA differs from that induced by sensitisation with environmental/bowel microorganisms.

T cell-mediated response to mycobacterial antigens has been implicated in the pathogenesis of inflammatory arthritis both in experimental animal models and in man. In adjuvant arthritis in rats, it has been established that the disease can be initiated by T cell clones specific for the 65-kDa mycobacterial heat-shock protein. Rats may also be protected to subsequent adjuvant arthritis induction by pre-immunisation with either a 65 KDa specific T cell line or with the hsp itself (Van Eden et al., Nature, 1988, 331:171 and Holoshitz et al., Science 1983, 219:56).

The epitope recognised by the arthritogenic T cell clone has been localized to amino acids 180-188. EP-A-322990 describes polypeptides having amino acid sequence 172-192 of a bacterial hsp65 and their use as immunogens for inducing resistance to auto-immune disease. WO 92/04049 discloses that a peptide comprising the amino acid

sequence corresponding to positions 180-186 of the Mycobacterium tuberculosis protein hsp65 is effective in the prevention and treatment of immune-related disease such as autoimmune arthritis.

Using the PIA model, it has been found (Thompson et al. Eur. J. Immunology, 1990, 20: 2479-2484) that autoimmune reactions to an antigen which cross-reacts with hsp65 are generated in pristane-induced arthritis. Furthermore, pre-immunisation with hsp65 has been shown to protect mice from the development of pristane-induced arthritis by altering the specificity or quality of the immune response to this antigen.

On further study using the PIA model, the applicants were surprised to find that a region of the microbial protein hsp65 quite different and remote from that described in for example WO 92/04049 is effective in providing a protective response against arthritis.

The present invention provides a polypeptide of 9 or more amino acid residues which comprises the sequence

VVNKIRG (SEQ ID 107)

or a homologue or functional equivalent or mimetic thereof.

The polypeptide may preferably consist of up to a total of 21 amino acid residues, more preferably it may consist of 9 to 11 residues.

The 7-mer sequence defined above (or its homologous or functional equivalents or mimetics) may be referred to hereafter as "the motif" of the present invention. This motif corresponds to the sequence 261-267 of microbial (mycobacterial) hsp65.

The invention also provides a polypeptide of up to 21 amino acid residues which comprises or consists of the sequence

VVNKIRGTFKS (SEQ ID 108)

or a homologue or functional equivalent or mimetic thereof. The above-described polypeptide sequence corresponds to amino acids 261-271 of microbial hsp65. The full sequence of microbial hsp65 is shown for example in EP-A-262 710. Although this reference describes a microbial hsp65 from Mycobacterium bovis, there is substantial sequence homology between microbial hsp65s, (generally in excess of 60% and up to 98%) and so the corresponding region of any microbial hsp65 can be identified and falls within the scope of the present invention.

Examples of the polypeptides of the invention also include fragments of microbial hsp65 protein including the motif, such as amino acid residues 251-267 (SEQ ID 51).

The polypeptides of the invention have been found to have a protective effect against auto-immune disease and in particular against the onset of RA when used in a preimmunisation procedure. In view of the fact that

these polypeptides, presented in this way would be expected to induce T_H2 cells, they would also be of use in the treatment of RA. Hence the invention further provides a vaccine for the prophylactic or therapeutic immunisation of a patient against auto-immune disease such as RA, which vaccine comprises a polypeptide as described above.

The polypeptide is suitably administered parenterally for example sub-cutaneously, intramuscularly, intravenously or intraperitoneally.

The polypeptide may also be administered in a trans-mucosal membrane manner, for example orally or nasally or in the form of a suppository.

The polypeptides of the invention are suitably administered in the form of a pharmaceutical composition in combination with a pharmaceutically acceptable carrier or excipient. Such compositions form a further aspect of the invention.

Suitable carriers include liquid carriers such as oils or water.

Suitable carriers also include solid carriers which may, for example, provide formulations including tablets or suspensions for oral administration or suppositories.

The compositions or formulations including the polypeptide of the invention as active ingredient may be adapted for nasal administration by inhalers, atomizers or sprays as are available in the art.

The polypeptides of the invention can be produced using various techniques which would be apparent to the skilled person. For example, they may be obtained by fragmentation of microbial hsp65 using conventional techniques after which the desired fragments obtained by purification, again using techniques which are known in the art. However peptides obtained by this method are less likely to have the precisely the desired length.

Alternatively, the polypeptides may be obtained using recombinant DNA technology. The nucleotide sequence encoding the desired polypeptide can be incorporated into a suitable host using a vector system which causes expression of the polypeptide.

Preferably however, polypeptides sequences may be generated entirely synthetically using standard chemical methods or peptide synthesizers available in the art.

As used herein, the expression 'homologue' refers to peptides having an amino acid sequence which is are at least 60%, preferably 70% and most preferably at least 80% homologous to the described polypeptide. The

expression 'functional equivalent' or 'mimetic' relates to any chemical, which may be a peptide or other organic chemical which produces similar effects in vivo to the compounds of the present invention. In particular, such compounds will produce a protective immunogenic response against RA which is better than that obtained using whole hsp65 when applied in pristane-induced arthritis model using tests as described in the examples hereinafter.

The invention will now be particularly described by way of example with reference to the accompanying drawings in which:

Figure 1 is the peptide library comprising eleven pools of overlapping peptides corresponding to the entire sequence of microbial hsp65 which are used in the examples;

Figure 2 shows a comparison of the proliferative response of T cells from each of 6 arthritic mice (top panel), 6 protected mice (middle panel) and 6 normal mice (n=6) to the eleven pools of overlapping peptides defined in Figure 1;

Figure 3 shows the results of an experiment to investigate the stimulation of T-cell responses in-vitro from hsp65 pre-immunised mice using a peptide derived from microbial hsp65;

Figure 4 shows the results of studies to determine the protection against PIA of mice pre-immunised with certain polypeptides.

Figure 5 shows the therapeutic effect of immunisation with a polypeptide including the motif of the invention at 60 days post pristane injection (D=60);

Figure 6 shows the prophylactic effect of pre-immunisation with a polypeptide including the motif of the invention at 10 days prior to pristane injection (D=-10);

Figure 7 shows the effect of adding increasing amounts of "Cold" viral Haemagglutinin upon binding of 20μg of biotinylated polypeptide (hsp 261-271: SEQ ID 108) to class II receptors on human EBV-transformed B-cell lines;

Figure 8 shows dose-dependant binding of biotinylated polypeptide (hsp 261-271: SEQ ID 108) to class II receptors on human EBV-transformed B-cell lines; and

Figure 9 shows the cytokine profile of T cells stimulated with peptide fragment hsp 261-271 of the invention or whole hsp65.

The following examples illustrate the invention.

Example 1

Proliferation of T cells *in-vitro* from PIA mice, hsp65 protected mice and normal age-matched mice.

Animals. Male CBA/Igb mice aged between 4 and 8 weeks were used unless otherwise specified. CBA/Igb mice were obtained by back-crossing (101 strain x CBA) F1 hybrids to CBA mice and selecting those mice with Igb allotype in their serum.

Arthritis induction by pristane. One group of six mice were immunised intraperitoneally with 50 micrograms of mycobacterial hsp65 administered as an emulsion in incomplete Freuds adjuvant (IFA). This group formed the protected group of mice. After ten days, this group and a further group of 6 mice received two intraperitoneal injections of 0.5ml of pristane 50 days apart (Aldrich Chemical Co., Milwaukee, WI.) in order to induce arthritis. A final group of 'normal' mice were maintained as controls.

Synthetic peptides used as antigens in immunisation studies. A library consisting of 106 overlapping peptides, representing the complete sequence of microbial hsp65, of between 15 and 19 amino acids in length, was synthesised using a simultaneous multiple-peptide solid phase synthetic method [Houghton R.A. Proc. Natl. Acad.

Sci. USA. (1985) 82:5131] using a polyamide resin [Arshady et al, J. Chem. Soc. Perkin Trans. (1981) I.529] and FMOC chemistry. The complete library is shown in Figure 1. Completed peptides were extracted from the resin using trifluoroacetic acid and suitable scavengers, and isolated by solvent evaporation and precipitation with methanol and diethylether. Purity was checked by amino acid analysis and by HPLC. Irrelevant control antigens BSA and human IgG were also used along with the mitogen ConA.

Eleven antigens were prepared, each comprising a pool of the groups of polypeptides, set out in Figure 1 as groups 1-11.

Preparation of T-cells and APC for culture. After 200 days, spleens of individual mice were aseptically removed and single cell suspensions made in a Petri dish containing RPMI-1640 medium supplemented with 20mM HEPES (pH 7.2, Flow Labs). Erythrocytes were removed by treating the spleen cells with 0.83% (w/v) NH_4Cl solution buffered with Tris (pH 7.2). After washing, cells were suspended in RPMI-1640 HEPES at 1.25 x 10^7cells/ml. Responder T cells were enriched according to the panning method of Engleman et al [Engleman et al. J. Immunol. (1981) 127:2124]. Briefly, 10cm diameter Petri dishes (Sterilin Ltd., Hounslow, GB) were coated with 5ml of 0.5 mg/ml mouse γ-globulin in PBS at room temperature for 2 hrs. After washing once with PBS, Petri dishes were

incubated with 5ml of a 1/100 dilution of rabbit anti-mouse Ig serum at 4°C overnight. After washing, 8ml of the spleen cell suspensions ($1x10^8$cells) were poured into the mouse Ig-rabbit anti-mouse Ig coated Petri dishes and incubated at room temperature for 40 mins. The nonadherent cells were then gently aspirated followed by washing with medium. These cells were then used as the T cell enriched fractions. A purity of .85% was achieved as assessed by anti-Thy 1.2 staining using flow cytometry (FACScan, Becton Dickinson Ltd., Oxford, GB). Normal mouse spleen cells were used as antigen presenting cells. In these experiments the APC were irradiated 1000 rads from a caesium source (Gravatom Industries, Gosport, GB).

Culture and assay of proliferation. This was carried out as described in Thompson et al., supra. The medium employed was alpha modification of Eagle's medium (alpha MEM) (Flow) supplemented with 4mM L-glutamine (Flow), 100U/ml benzyl penicillin (Glaxo Ltd., Green ford, GB), 100µg/ml streptomycin sulphate (Evans Medical Ltd., Greenford, GB), 5 x 10^{-5}M2-mercaptoethanol (Sigma), 20 mM HEPES and 0.5% fresh normal mouse serum. The cultures consisted of 1.25 x 10^6 purified splenic T-cells plus 1.25 x 10^6 APC per ml, in a volume of 2ml in a 24 well plate (Flow) in the presence or absence of the various antigens 92.5-10µg/ml. Alternatively, some cultures were set up in a volume of 200µl in round bottom 96 well plates (Flow). All cultures were incubated at 37°C in a humidified atmosphere of 5% CO2 and 95% air.

After the periods of incubation indicated, triplicate 100microlitre samples of each of the 2 ml cultures were transferred to 96 well, round bottom culture plates (Flow) and pulsed with 2mCi of ^{3}H-Thymidine (specific activity 70-85 Ci/mMol; Amersham International Ltd., Amersham, GB) per well for 6 hours. The cells were then harvested onto glass fibre filter mats (Whatman Ltd., Maidstone, GB) using a multiple sample harvester (Skatron AS, Lier, Norway) and the ^{3}H-Thymidine incorporated into newly synthesized DNA measured using conventional liquid scintillation procedures with a LKB rackbeta counter (LKB-Wallac Ltd., Pharmacia, Uppsala, Sweden). The results are presented (Figure 2) as stimulation indices (S.I.= cpm test divided by cpm control without antigen). Positive stimulation resulted in maximal ^{3}H-Thymidine uptake of ~30,000 counts per minute.

It is clear from these results and specifically from the results obtained from the hsp65 protected group that polypeptides in group 6 produce the most significant stimulation of T cells.

This conclusion is reached because, with reference to the hsp65 protected group results of Figure 2, group 6 shows the most consistent increase in S.I. over the six test results. For example, taking a baseline at about S.I.=3, group 6 meets or exceeds this figure for 5 of 6 results. None of the other group pools gave such repeatable results.

Example 2

Proliferation of T cells *in-vitro* from hsp65 protected mice in the presence of polypeptide antigens.

Following the results in Example 1 above, a more detailed study was made of the preferred peptide in group 6 (hsp 261-271) and by way of comparison peptides were also included in the test which did not contain the motif (hsp 11-26 and hsp 251-266).

A group of hsp65 preimmunised or PIA protected animals were prepared in accordance with the procedures described in Example 1. Following essentially the same procedure, spleen cells from the mice were cultured and then challenged with antigen

and

the stimulation indices measured as described in Example 1. The results are shown in graph form in Figure 3. In figure 3, three sets of results are shown representing data on T-cell proliferation in cells respectively from: (1) normal animals (norm); (2) protected animals previously immunised with hsp65 (imm65); and (3) animals with pristane induced arthritis (PIA). For each set the columns represent respectively:

(1) whole hsp65;

(2) fragment hsp 251-266;

(3) fragment hsp 261-271 according to the invention;

(4) fragment hsp 11-26.

It is clear from this experiment that data sets two and three (imm65 and PIA) demonstrate the ability of a polypeptide of the invention to produce a T-cell proliferation essentially equivalent to that produced by stimulation with whole hsp65. This indicates that the peptide used includes an immunodominant T-cell epitope. Such an immunodominant epitope is important for immunological purposes.

Example 3

Protection of mice against PIA by immunisation with microbial Hsp65 fragments

Animals. Male CBA/Igb mice aged between 4 and 8 weeks as described in Example 1 were used unless otherwise specified.

Immunisation of animals. Groups of mice were immunised intraperitoneally 10 days before pristane challenge as follows:

Group	No. mice	pre-immunisation polypeptide
1	21 (6 weeks old)	-
2	21 (10 weeks old)	-
3	21	polypeptide corresponding to amino acids 261-271 of microbial hsp 65
4	15	whole microbial hsp65

50 Micrograms of each polypeptide was administered as an emulsion in IFA. The polypeptide fragments used in the pre-immunisation of group 3 was manufactured by Cambridge Research Biochemicals of Northwich, Cheshire, UK.

Arthritis induction by pristane. Arthritis was then induced as described in Example 1 by two intraperitoneal injections of 0.5ml of pristane 50 days apart. The animals were examined for the incidence of arthritis in the ankle joints at various time points. The final incidence was assessed 200 days post pristane injection. The arthritis was assessed by measuring the ankle joints with a micrometer. In CBA/Ig^b mice the swollen joints ranged in size from 3.0-4.0mm compared with normal joints which had a range from 2.5-2.8mm. However, this difference could easily be distinguished, and in most experiments the joints were assessed visually, arthritis being scored at present or absent [Thompson et al, Eur. J. Immunol. (1990) 20:2479 and Barker et al, Autoimmunity. (1992) 14:73].

The percentage of animals in each group which developed arthritis after a period of 200 days is shown in Figure 4. It is clear that the peptide region corresponding to region 261-271 generates an improved protective effect against RA in mice compared to whole hsp65 and confirms that this sequence, which is

VVNKIRGTFKS (SEQ ID 108)

is effective in producing a beneficial effect.

Further evidence of the effect of hsp peptide fragment 261-271 (containing the motif of the invention) on pristane induced arthritis is presented in Figures 5 and 6.

Figure 5 shows the results of an experiment to assess the therapeutic efficacy of a peptide according to the invention in treatment of PIA. 50 microgrammes of peptide was administered ip as an emulsion in IFA to each mouse at day 60. This treatment followed two pristane injections, 50 days apart, one at day 0 and one at day 50. Day 60 is judged to be the stage just prior to the development/onset phase of PIA. Strikingly, the polypeptide hsp 261-271 appears to have completely prevented the onset of PIA symptoms in all mice. The percentage arthritis was assessed both by visual scoring and histological scoring.

Figure 6 shows the results of an experiment to assess the prophylactic efficacy of a peptide according to the invention in prevention of PIA. In this case peptide was administered 10 days prior to the first pristane injection (day -10). Subsequently two pristane injections were given 50 days apart, one at day 0 and one at day 50. The results show that pre-immunisation with peptide according to the invention significantly reduces the percentage of arthritis.

Evidence on the ability of polypeptide according to the invention to bind to MHC class II receptors is presented in Figures 7 and 8.

In Figure 7 there is shown the effect of adding increasing amounts of "Cold" viral Haemagglutinin upon the binding of 20 microgrammes of biotinylated peptide fragment hsp 261-271 to class II on human EBV-transformed B-cell lines. Figure 7 shows the effects of increasing dose of non-biotinylated ("Cold") viral Haemagglutinin (which binds indiscriminately to class II receptors) upon the percentage binding by a fixed concentration of biotinylated hsp 261-271. The results show good binding potential/avidity to class II receptors, as evidenced by the data which shows that the "Cold" viral Haemagglutinin does not inhibit the percentage binding by biotinylated hsp 261-271 in a dose-dependent manner.

Figure 8 shows the dose-dependent binding of biotinylated hsp 261-271 to either the SW or SF cell lines. The SW B-cell line has a greater affinity for the peptide, with peak binding (about 60%) occurring at 50 microgrammes peptide. At higher doses of peptide the percentage binding decreases. The SF B-cell line binds little or no peptide at concentrations up to 50 microgrammes, after which the

percentage binding increases with concentration of peptide utilised. Interestingly, the data from Figures 7 and 8 appears to show that, at low concentrations, viral Haemagglutinin actually potentiates the binding of the biotinylated peptide to both cell lines (e.g. see the increase in Figure 8 for the SW cell line at 20 microgrammes peptide the binding is increased by 20 microgrammes viral Haemagglutinin: for the SF cell line for 20 microgrammes peptide the binding is increased from 0 by between 30 and 50 microgrammes viral Haemagglutinin).

For Figures 7 and 8, the percentage binding to the populations of B-cells was determined using extrAvidin-FITC (Sigma) and FACS analysis.

Figure 9 shows results from an experiment to determine the cytokine profile of T-cells from mice in response to various stimulation protocols.

The first two sets of data in figure 3 represent cytokine profiles of T-cells pre-immunised with native hsp65 prior to pristane injection and restimulated either with peptide hsp 261-271 (hsp (PEP)) or with native hsp (hsp(hsp)) whilst in co-culture with APCs. The data presented in sets 3 and 4

represents a protocol comprising pristane injection followed by stimulation with peptide 261-267 (IPP(pep)) or pristane injection followed by stimulation with native hsp (IPP(hsp)) whilst in co-culture with APCs.

In each case, the data of particular interest and significance is represented by the second bar, indicating production of the Th2 anti-inflammatory cytokine IL-4. It is important to note that hsp(pep) produces an approximately 3 fold increase in IL4 compared to hsp(hsp), and IPP(pep) produces an approximately 2 fold increase in IL4 compared to IPP(hsp). In each case measurement of the amount of cytokine released was by ELISA.

The applicants believe that the role of microbial hsp's in both the induction of arthritis and protection against the disease may be due to the form of antigen presentation. Depending upon this, either T_H1 cells are induced which leads to pristane induced arthritis due to determinant spreading, or T_H2 cells are induced which leads to protection due to repertoire limitation. This gives rise to the possibility of devising methods for the prophylaxis or treatment of arthritis and other auto-immune disease.

SEQUENCE LISTING

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(ii) TITLE OF INVENTION: Polypeptides and their use in the prophylaxis and treatment of auto-immune disease

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(vi) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: GB 9419553.4
(B) FILING DATE: 27-SEP-1994

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Met Ala Lys Thr Ile Ala Tyr Asp Glu Glu Ala Arg Arg Gly Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Ala Tyr Asp Glu Glu Ala Arg Arg Gly Leu Glu Arg Gly Leu Asn Ser
1 5 10 15

Leu

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Ala Arg Arg Gly Leu Glu Arg Gly Leu Asn Ser Leu Ala Asp Ala Val
1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Glu Arg Gly Leu Asn Ser Leu Ala Asp Ala Val Lys Val Thr Leu Gly
1 5 10 15

Pro Lys Gly

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Ser Leu Ala Asp Ala Val Lys Val Thr Leu Gly Pro Lys Gly Arg Asn
1 5 10 15

Val

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Val Lys Val Thr Leu Gly Pro Lys Gly Arg Asn Val Val Leu Glu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Gly Pro Lys Gly Arg Asn Val Val Leu Glu Lys Lys Trp Gly Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Asn Val Val Leu Glu Lys Lys Trp Gly Ala Pro Thr Ile Thr Asn Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Lys Lys Trp Gly Ala Pro Thr Ile Thr Asn Asp Gly Val Ser Ile
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Pro Thr Ile Thr Asn Asp Gly Val Ser Ile Ala Lys Glu Ile Glu Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Asp Gly Tyr Ser Ile Ala Lys Glu Ile Glu Leu Glu Asp Pro Tyr Glu

1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Ala Lys Glu Ile Glu Leu Glu Asp Pro Tyr Glu Lys Ile Gly Ala Glu
1 5 10 15

Leu Val Lys

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Leu Glu Asp Pro Tyr Glu Lys Ile Gly Ala Glu Leu Val Lys Glu Val
1 5 10 15

Ala Lys

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Glu Lys Ile Gly Ala Glu Leu Val Lys Glu Val Ala Lys Lys Thr Asp
1 5 10 15

Asp Val Ala

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Glu Leu Val Lys Glu Val Ala Lys Lys Thr Asp Asp Val Ala Gly Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Val Ala Lys Lys Thr Asp Asp Val Ala Gly Asp Gly Thr Thr Thr Ala
1 5 10 15

Thr Val Leu

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Asp Asp Val Ala Gly Asp Asp Thr Thr Thr Ala Thr Val Leu Ala Gln
1 5 10 15

Leu Ala Val

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Asp Gly Thr Thr Thr Ala Thr Val Leu Ala Gln Ala Leu Val Lys Glu
1 5 10 15

Gly Leu

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

Ala Thr Val Leu Ala Gln Ala Leu Val Lys Glu Gly Leu Arg Asn Val
1 5 10 15

Ala Ala Gly Ala
20

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

Gln Ala Leu Val Lys Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn
1 5 10 15

Pro Leu Gly

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn Pro Leu Gly Leu Lys
1 5 10 15

Arg Gly

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Val Ala Ala Gly Ala Asn Pro Leu Gly Leu Lys Arg Gly Ile Glu Lys
1 5 10 15

Ala

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Asn Pro Leu Gly Leu Lys Arg Gly Ile Glu Lys Ala Val Asp Lys Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Lys Arg Gly Ile Glu Lys Ala Val Asp Lys Val Thr Glu Thr Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

Lys Ala Val Asp Lys Val Thr Glu Thr Leu Leu Lys Asp Ala Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Val Thr Glu Thr Leu Leu Lys Asp Ala Lys Glu Val Glu Thr Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Leu Lys Glu Asp Lys Glu Val Glu Thr Lys Glu Gln Ile Ala Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Glu Val Glu Thr Lys Glu Gln Ile Ala Ala Thr Ala Ala Ile Ser Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

Gln Ile Ala Ala Thr Ala Ala Ile Ser Ala Gly Asp Gln Ser Ile Gly
1 5 10 15

Asp

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

Thr Ala Ala Ile Ser Ala Gly Asp Gln Ser Ile Gly Asp Leu Ile
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

Ala Gly Asp Gln Ser Ile Gly Asp Leu Ile Ala Glu Ala Met Asp Lys
1 5 10 15

Val Gly

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

Ile Gly Asp Leu Ile Ala Glu Ala Met Asp Lys Val Gly Asn Glu Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

Ala Glu Ala Met Asp Lys Val Gly Asn Glu Gly Val Ile Thr Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Lys Val Gly Asn Glu Gly Val Ile Thr Val Glu Glu Ser Asn Thr Phe
1 5 10 15

Gly Leu

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

Gly Val Ile Thr Val Glu Glu Ser Asn Thr Phe Gly Leu Gln Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

Glu Glu Ser Asn Thr Phe Gly Leu Gln Leu Glu Leu Thr Glu Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

Phe Gly Leu Gln Leu Glu Leu Thr Glu Gly Met Arg Phe Asp Lys Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

Glu Leu Thr Glu Gly Met Arg Phe Asp Lys Gly Tyr Ile Ser Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

Met Arg Phe Asp Lys Gly Tyr Ile Ser Gly Tyr Phe Val Thr Asp Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

Gly Tyr Ile Ser Gly Tyr Phe Val Thr Asp Ala Glu Arg Gln Glu Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

Tyr Phe Val Thr Asp Ala Glu Arg Gln Glu Ala Val Leu Glu Glu Pro
1 5 10 15

Tyr Ile

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

Ala Glu Arg Gln Glu Ala Val Leu Glu Glu Pro Tyr Ile Leu Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

Ala Val Leu Glu Glu Pro Tyr Ile Leu Leu Val Ser Ser Lys Val Ser
1 5 10 15

Thr Val Lys

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

Pro Tyr Ile Leu Leu Val Ser Ser Lys Val Ser Thr Val Lys Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

Val Ser Ser Lys Val Ser Thr Val Lys Asp Leu Leu Pro Leu Leu Glu
1 5 10 15

Lys Val

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

Ser Thr Val Lys Asp Leu Leu Pro Leu Leu Glu Lys Val Ile Gln Ala
1 5 10 15

Gly Lys

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

Leu Leu Pro Leu Leu Glu Lys Val Ile Gln Ala Gly Lys Ser Leu Leu
1 5 10 15

Ile Ile Ala

(2) INFORMATION FOR SEQ ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

Glu Lys Val Ile Gln Ala Gly Lys Ser Leu Leu Ile Ile Ala Glu Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

Ala Gly Lys Ser Leu Leu Ile Ile Ala Glu Asp Val Glu Gly Glu Ala
1 5 10 15

Leu

(2) INFORMATION FOR SEQ ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Leu Ile Ile Ala Glu Asp Val Glu Gly Glu Ala Leu Ser Thr Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

Asp Val Glu Gly Glu Ala Leu Ser Thr Leu Val Val Asn Lys Ile Arg
1 5 10 15

Gly

(2) INFORMATION FOR SEQ ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

Ala Leu Ser Thr Leu Val Val Asn Lys Ile Arg Gly Thr Phe Lys Ser
1 5 10 15

Val Ala

(2) INFORMATION FOR SEQ ID NO: 53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

Val Val Asn Lys Ile Arg Gly Thr Phe Lys Ser Val Ala Val Lys Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

Arg Gly Thr Phe Lys Ser Val Ala Val Lys Ala Pro Gly Phe Gly Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

Ser Val Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met
1 5 10 15

Leu Gln Asp

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu Gln Asp Met Ala
1 5 10 15

Ile

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

Asp Arg Arg Lys Ala Met Leu Gln Asp Met Ala Ile Leu Thr Gly Ala
1 5 10 15

Gln Val

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

Met Leu Gln Asp Met Ala Ile Leu Thr Gly Ala Gln Val Ile Ser Glu
1 5 10 15

Glu Val Gly

(2) INFORMATION FOR SEQ ID NO: 59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

Ala Ile Leu Thr Gly Ala Gln Val Ile Ser Glu Glu Val Gly Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

Ala Gln Val Ile Ser Glu Glu Val Gly Leu Thr Leu Glu Asn Thr Asp
1 5 10 15

Leu

(2) INFORMATION FOR SEQ ID NO: 61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

Glu Glu Val Gly Leu Thr Leu Glu Asn Thr Asp Leu Ser Leu Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

Thr Leu Glu Asn Thr Asp Leu Ser Leu Leu Gly Lys Ala Arg Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

Asp Leu Ser Leu Leu Gly Lys Ala Arg Lys Val Val Met Thr Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

Gly Lys Ala Arg Lys Val Val Met Thr Lys Asp Glu Thr Thr Ile Val
1 5 10 15

Glu Gly

(2) INFORMATION FOR SEQ ID NO: 65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

Val Val Met Thr Lys Asp Glu Thr Thr Ile Val Glu Gly Ala Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

Asp Glu Thr Thr Ile Val Glu Gly Ala Gly Asp Thr Asp Ala Ile Ala
1 5 10 15

Gly

(2) INFORMATION FOR SEQ ID NO: 67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

Val Glu Gly Ala Gly Asp Thr Asp Ala Ile Ala Gly Arg Val Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

Asp Thr Asp Ala Ile Ala Gly Arg Val Ala Gln Ile Arg Thr Glu Ile
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

Ala Gly Arg Val Ala Gln Ile Arg Thr Glu Ile Glu Asn Ser Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

Gln Ile Arg Thr Glu Ile Glu Asn Ser Asp Ser Asp Tyr Asp Arg Glu
1 5 10 15

Lys Leu

(2) INFORMATION FOR SEQ ID NO: 71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

Ile Glu Asn Ser Asp Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg
1 5 10 15

Leu

(2) INFORMATION FOR SEQ ID NO: 72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg Leu Ala Lys Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

Glu Lys Leu Gln Glu Arg Leu Ala Lys Leu Ala Gly Gly Val Ala Val
1 5 10 15

Ile Lys

(2) INFORMATION FOR SEQ ID NO: 74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

Arg Leu Ala Lys Leu Ala Gly Gly Val Ala Val Ile Lys Ala Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

Ala Gly Gly Val Ala Val Ile Lys Ala Gly Ala Ala Thr Glu Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

Val Ile Lys Ala Gly Ala Ala Thr Glu Val Glu Leu Lys Glu Arg Lys
1 5 10 15

His Arg Ile

(2) INFORMATION FOR SEQ ID NO: 77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

Ala Ala Thr Glu Val Glu Leu Lys Ile Arg Lys His Arg Ile Glu Asp
1 5 10 15

Ala

(2) INFORMATION FOR SEQ ID NO: 78:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

Glu Leu Lys Glu Arg Lys His Arg Ile Glu Asp Ala Val Arg Asn Ala
1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO: 79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

Lys His Arg Ile Glu Asp Ala Val Arg Asn Ala Lys Ala Ala Val Glu
1 5 10 15

Glu Gly

(2) INFORMATION FOR SEQ ID NO: 80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

Asp Ala Val Arg Asn Ala Lys Ala Ala Val Glu Glu Gly Ile Val Ala
1 5 10 15

Gly

(2) INFORMATION FOR SEQ ID NO: 81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

Ala Lys Ala Ala Val Glu Glu Gly Ile Val Ala Gly Gly Gly Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

Glu Glu Gly Ile Val Ala Gly Gly Gly Val Thr Leu Leu Gln Ala Ala
1 5 10 15

Pro Ala Leu

(2) INFORMATION FOR SEQ ID NO: 83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:

Ala Gly Gly Gly Val Thr Leu Leu Gln Ala Ala Pro Ala Leu Asp Lys
1 5 10 15

Leu

(2) INFORMATION FOR SEQ ID NO: 84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

Thr Leu Leu Gln Ala Ala Pro Ala Leu Asp Lys Leu Lys Leu Thr Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

Ala Pro Ala Leu Asp Lys Leu Lys Leu Thr Gly Asp Glu Ala Thr Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

Lys Leu Lys Leu Thr Gly Asp Glu Ala Thr Gly Ala Asn Ile Val Lys
1 5 10 15

Val Ala

(2) INFORMATION FOR SEQ ID NO: 87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

Gly Asp Glu Ala Thr Gly Ala Asn Ile Val Lys Val Ala Leu Glu Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

Gly Ala Asn Ile Val Lys Val Ala Leu Glu Ala Pro Leu Lys Gln Ile
1 5 10 15

Ala

(2) INFORMATION FOR SEQ ID NO: 89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

Lys Val Ala Leu Glu Ala Pro Leu Lys Gln Ile Ala Phe Asn Ser Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

Ala Pro Leu Lys Gln Ile Ala Phe Asn Ser Gly Met Glu Pro Gly Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

Ile Ala Phe Asn Ser Gly Met Glu Pro Gly Val Val Ala Glu Lys Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

Gly Met Glu Pro Gly Val Val Ala Glu Lys Val Arg Asn Leu Ser Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

Val Val Ala Glu Lys Val Arg Asn Leu Ser Val Gly His Gly Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

Val Arg Asn Leu Ser Val Gly His Gly Leu Asn Ala Ala Thr Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

Val Gly His Gly Leu Asn Ala Ala Thr Gly Glu Tyr Glu Asp Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

Asn Ala Ala Thr Gly Glu Tyr Glu Asp Leu Leu Lys Ala Gly Val Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

Glu Tyr Glu Asp Leu Leu Lys Ala Gly Val Ala Asp Pro Val Lys Tyr
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

Leu Lys Ala Gly Val Ala Asp Pro Val Lys Val Thr Arg Ser Ala Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

Ala Asp Pro Val Lys Val Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser
1 5 10 15

Ile Ala Gly

(2) INFORMATION FOR SEQ ID NO: 100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

Val Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Ile Ala Gly Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

Leu Gln Asn Ala Ala Ser Ile Ala Gly Leu Phe Leu Thr Thr Glu Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

Ser Ile Ala Gly Leu Phe Leu Thr Thr Glu Ala Val Val Ala Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

Phe Leu Thr Thr Glu Ala Val Val Ala Asp Lys Pro Glu Lys Thr Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:

Ala Val Val Ala Asp Lys Pro Glu Lys Thr Ala Ala Pro Ala Ser Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:

Lys Pro Glu Lys Thr Ala Ala Pro Ala Ser Asp Pro Thr Gly Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:

Ala Ala Pro Ala Ser Asp Pro Thr Gly Gly Met Gly Gly Met Asp Phe
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107:

Val Val Asn Lys Ile Arg Gly
1 5

(2) INFORMATION FOR SEQ ID NO: 108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108:

Val Val Asn Lys Ile Arg Gly Thr Phe Lys Ser
1 5 10

Claims

1. A polypeptide of 9 or more amino acid residues which comprises the sequence VVNKIRG (SEQ ID 107) or a homologue or functional equivalent or mimetic thereof.

2. A polypeptide according to claim 1 which consists of up to a total of 21 amino acid residues.

3. A polypeptide according to claim 1 which consists of 9, 10 or 11 amino acid residues.

4. A polypeptide according to claim 1 or 2 which comprises the sequence VVNKIRGTFKS (SEQ ID 108) or a homologue or functional equivalent or mimetic thereof.

5. A polypeptide according to claim 1 which consists of the sequence VVNKIRGTFKS (SEG ID 108) or a homologue or functional equivalent or mimetic thereof.

6. A pharmaceutical composition which comprises a polypeptide according to any of claims 1 to 5 in combination with a pharmaceutical acceptable carrier or excipient.

7. Use of a pharmaceutical composition according to claim 6 in prophylaxis of auto-immune disease.

8. Use of a pharmaceutical composition according to claim 6 in treatment of auto-immune disease.

9. A process for producing a polypeptide according to any one of claims 1 to 5 which process includes the steps of fragmentation of microbial heat shock protein hsp65 and isolation and/or purification of the desired polypeptide fragment.

10. A process for producing a polypeptide according to any one of claims 1 to 5 using recombinant DNA technology which process includes the steps of incorporating a nucleotide sequence encoding the desired polypeptide into a suitable host using a vector system and causing expression of the polypeptide and isolation and/or purification of the polypeptide.

11. A process for producing a polypeptide according to any one of claims 1 to 5 which process includes a step of chemically synthetically combining amino acids or amino acid sequences to form the desired polypeptide.

12. Use of a polypeptide according to any one of claims 1 to 5 in the manufacture of a medicament for the prophylaxis of auto-immune disease.

13. Use of a polypeptide according to any one of claims 1 to 5 in the manufacture of a medicament for the treatment of auto-immune disease.

14. A method of prophylaxis of auto-immune disease which method comprises administering to a patient an effective amount of a polypeptide according to any one of claims 1 to 5 or a pharmaceutical composition according to claim 6.

15. A method of treatment of auto-immune disease which method comprises administering to a patient an effective amount of a polypeptide according to any of claims 1 to 5 or a pharmaceutical composition according to claim 6.

GROUP	SEQ ID NO.	SEQUENCE
1	1	MAKTLAYDEEARRGL
	2	AYDEEARRGLERGLNSL
	3	ARRGLERGLNSLADAVK
	4	ERGLNSLADAVKVTLGPKG
	5	SLADAVKVTLGPKGRNV
	6	VKVTLGPKGRNVVLEK
	7	GPKGRNVVLEKKWGA
	8	NVVLEKKWGAPTITND
	9	KKWGAPTITNDGVSI
	10	PTITNDGVSLAKEIEL
2	11	DGYSLAKEIELEDPYEK
	12	AKEIELEDPYEKIGAELVK
	13	LEDPYEKIGAELVKEVAK
	14	EKIGAELVKEVAKKTDDVA
	15	ELVKEVAKKTDDVAGD
	16	VAKKTDDVAGDGTTTATVL
	17	DDVAGDGTTTATVLAQALV
	18	DGTTTATVLAQALVKEGL
	19	ATVLAQALVKEGLRNVAAGA
	20	QALVKEGLRNVAAGANPLG
3	21	EGLRNVAAGANPLGLKRG
	22	VAAGANPLGLKRGIEKA
	23	NPLGLKRGIEKAVDKV
	24	KRGIEKAVDKVTETL
	25	KAVDKVTETLLKDAK
	26	VTETLLKDAKEVETK
	27	LKDAKEVETKEQLAA
	28	EVETKEQLAATAAISA
	29	QLAATAAISAGDQSIGD
4	30	TAAISAGDQSIGDLI
	31	AGDQSIGDLIAEAMDKVG
	32	IGDLIAEAMDKVGNEG
	33	AEAMDKVGNEGVTTV
	34	KVGNEGVITVEESNTFGL
	35	GVITVEESNTFGLQL
	36	EESNTFGLQLELTEG
	37	FGLQLELTEGMRFDKG
	38	ELTEGMRFDKGYISG
	39	MRFDKGYISGYFVTDA
	40	GYISGYFVTDAERQEA

FIGURE 1(a)

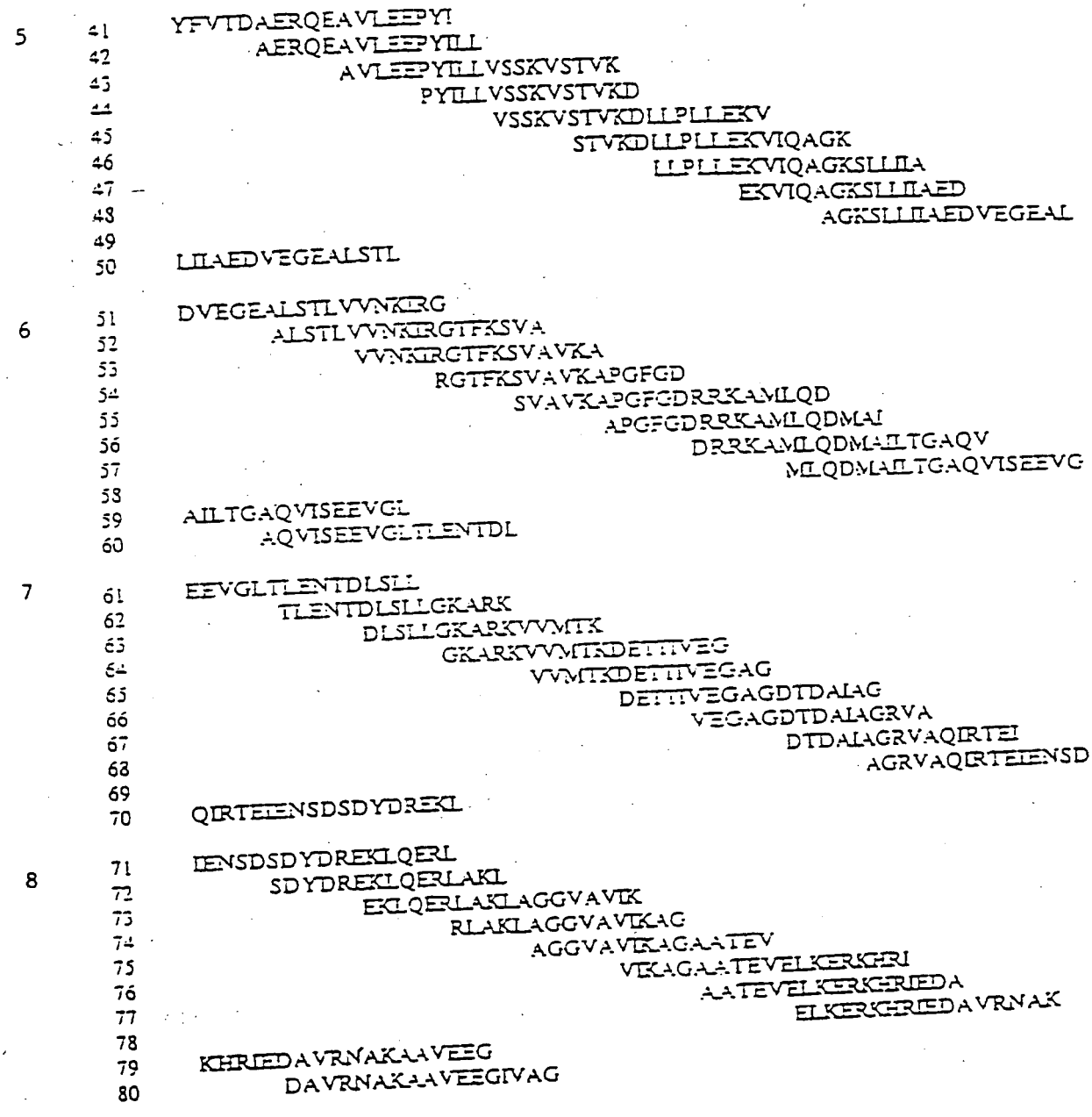


FIGURE 1(b)

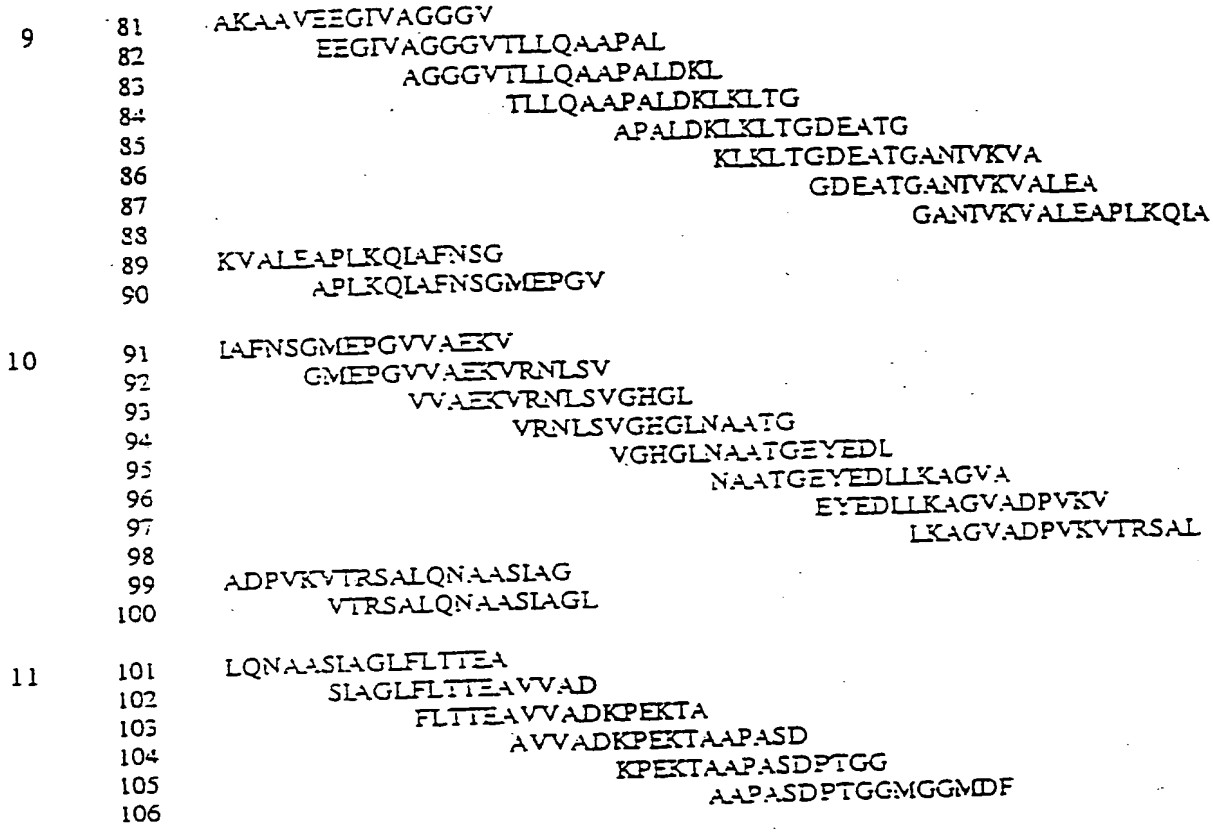


FIGURE 1(c)

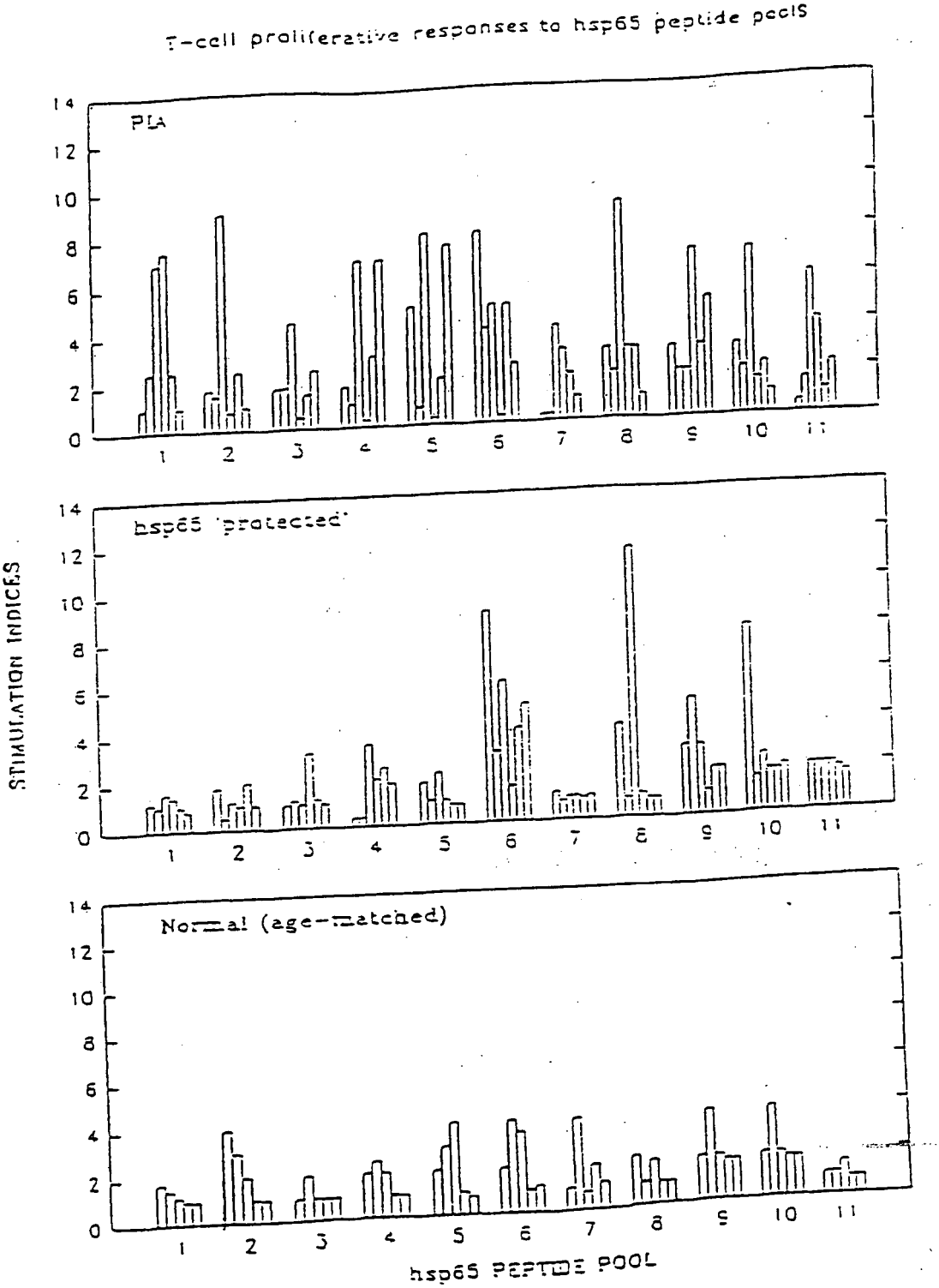


FIGURE 2

FIGURE 3

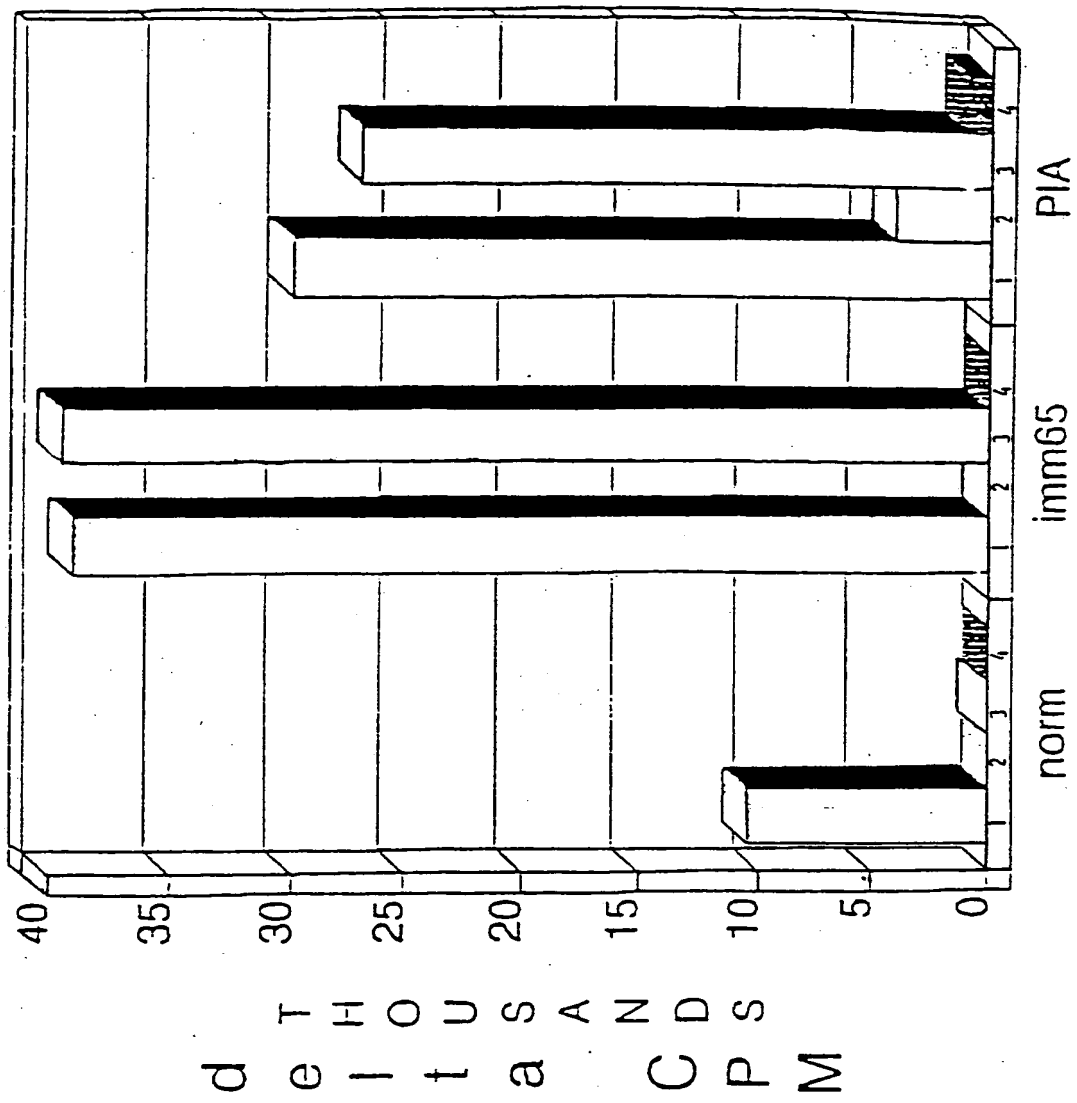
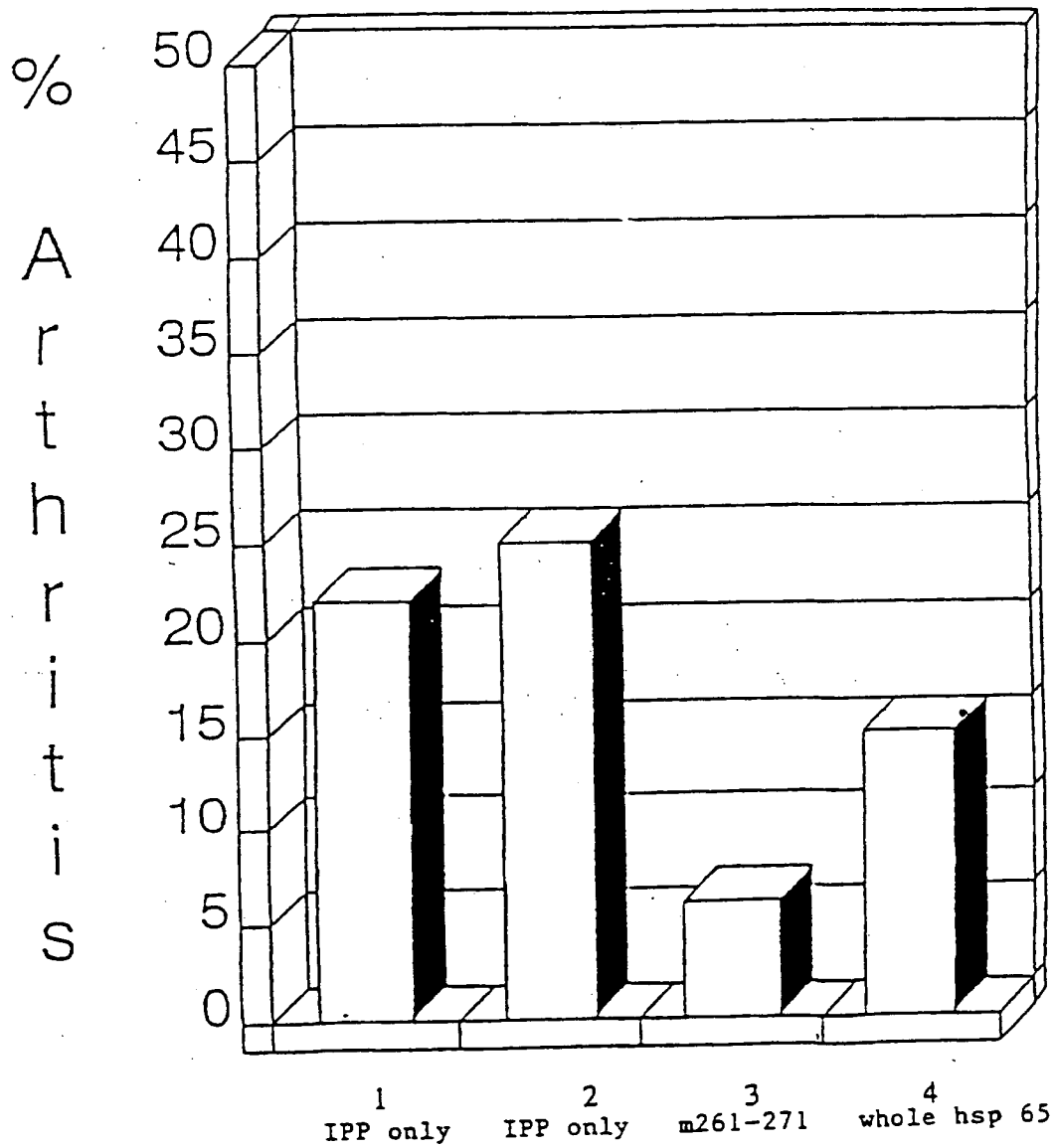


FIGURE 4



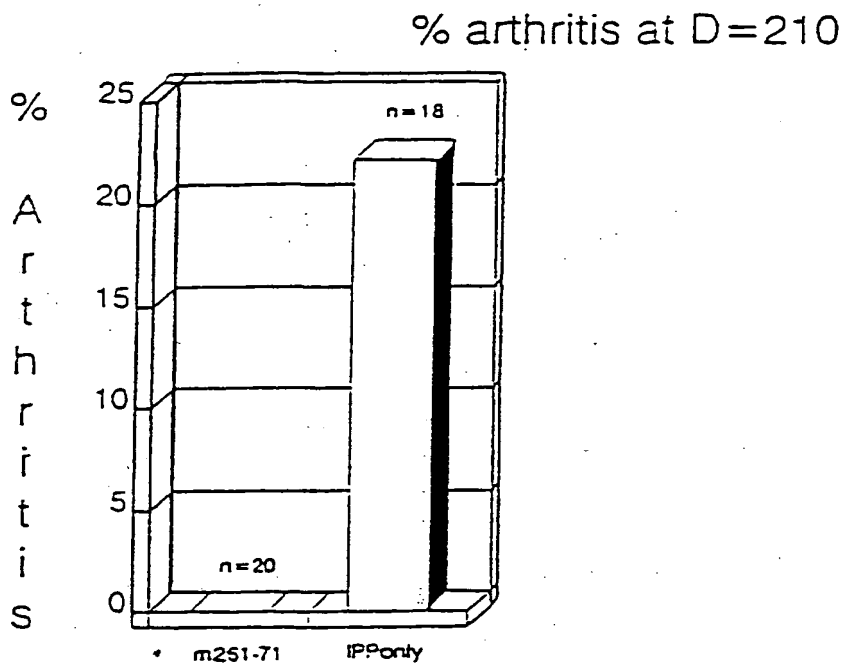


FIGURE 5

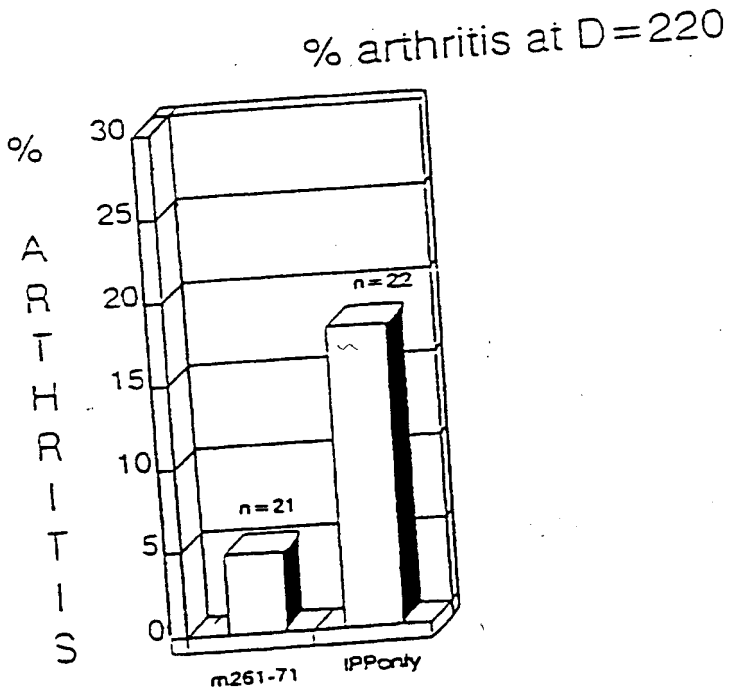


FIGURE 6

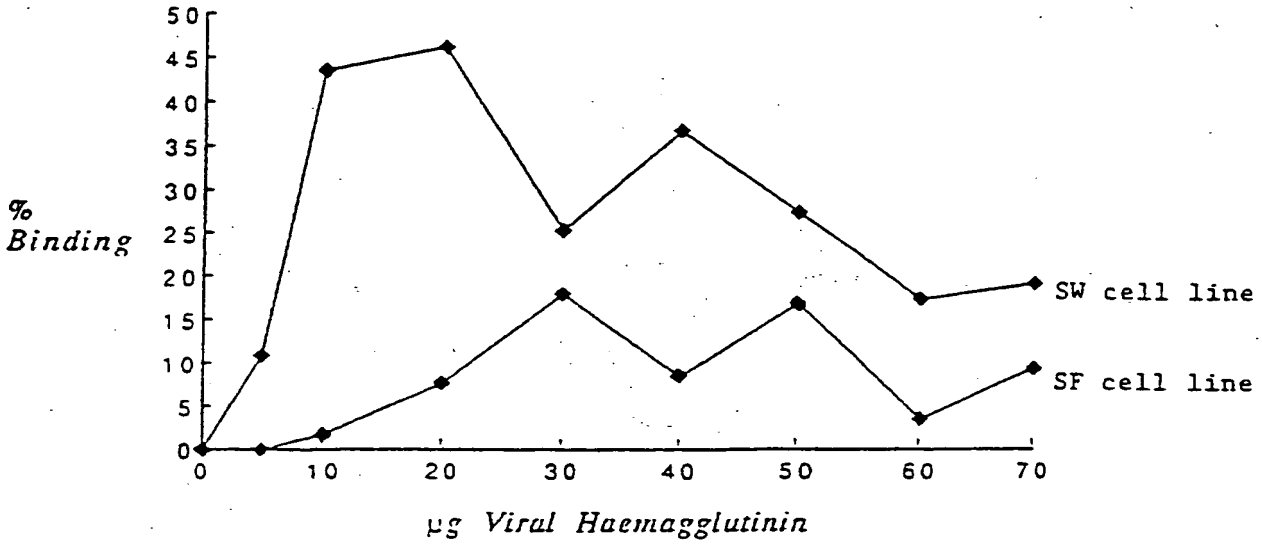
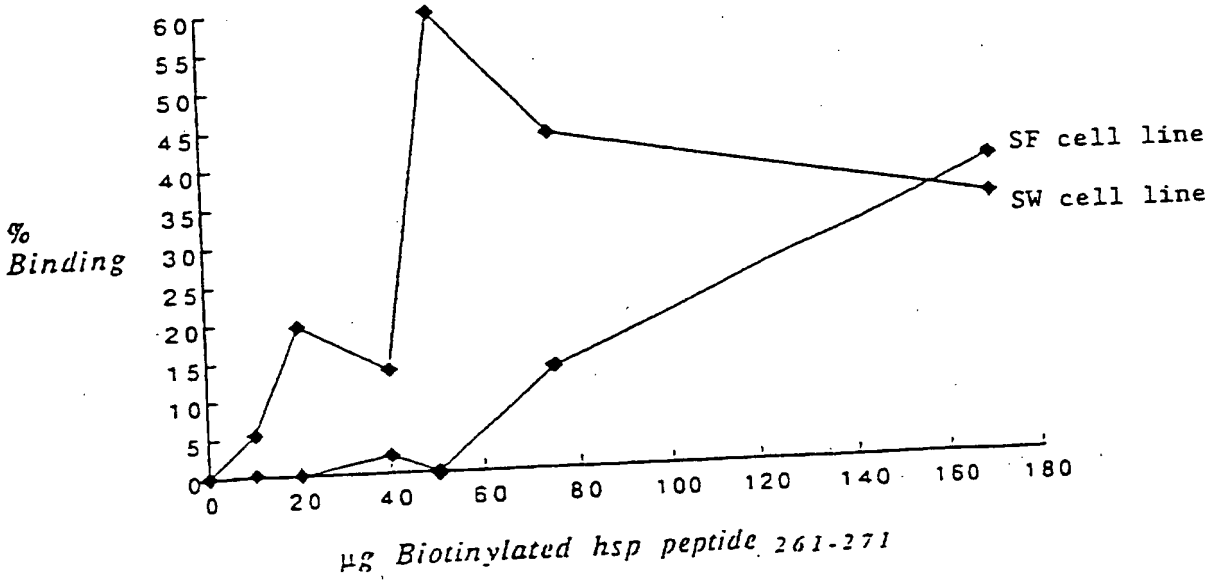


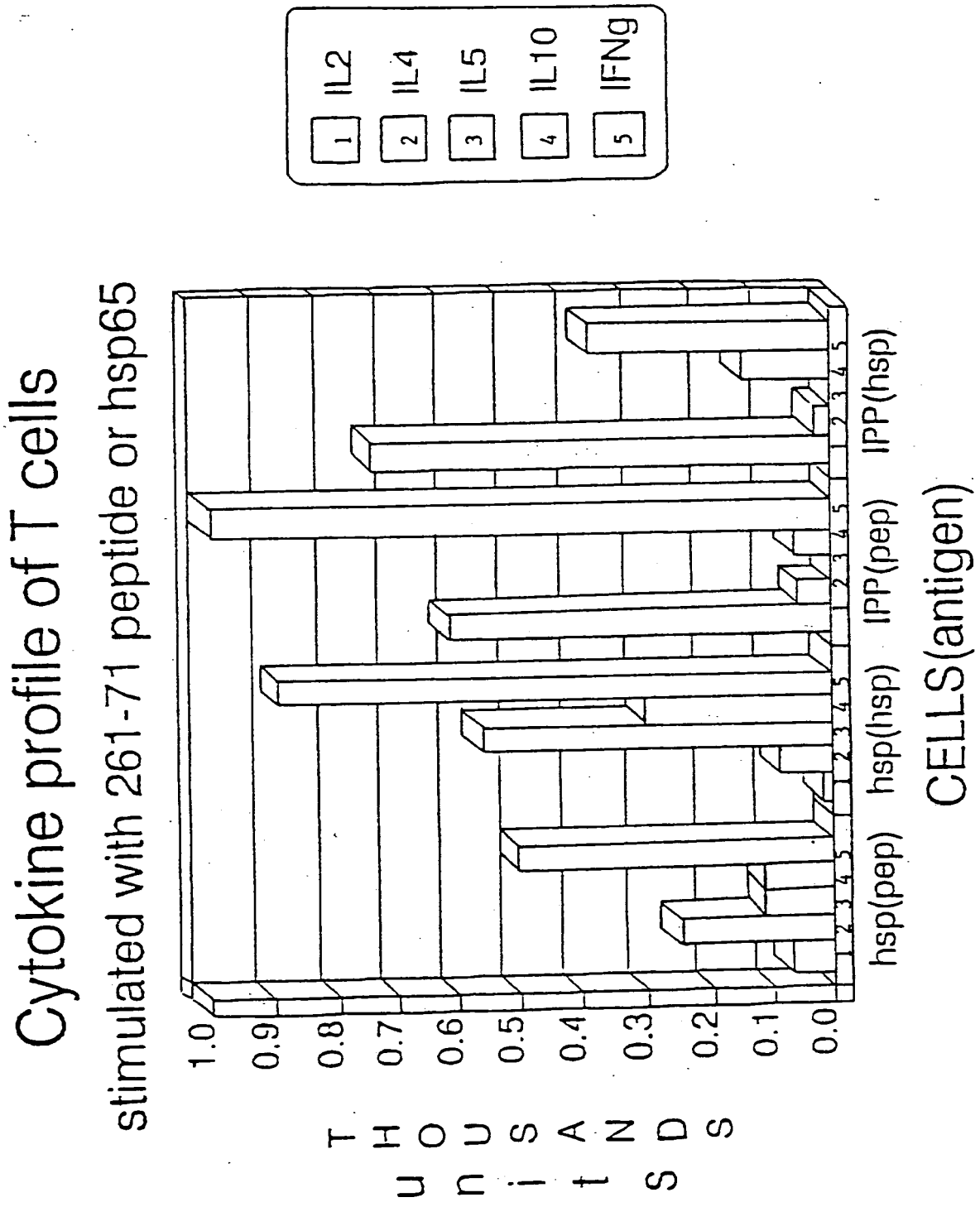
FIGURE 7



NB : The Concentrations Of Peptides Are µg per 250 µl.

FIGURE 8

FIGURE 9



Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9010449	20-09-90	US-A-	5114844	19-05-92
		AU-B-	639456	29-07-93
		AU-B-	5546790	09-10-90
		CA-A-	2029861	15-09-90
		EP-A-	0417271	20-03-91
		JP-T-	4502920	28-05-92
WO-A-9204049	19-03-92	AU-B-	650065	09-06-94
		AU-B-	8755991	30-03-92
		EP-A-	0503055	16-09-92
WO-A-9525744	28-09-95	AU-B-	1962895	09-10-95

INTERNATIONAL SEARCH REPORT

...al application No.
PCT/GB95/02295

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7,8,14,15
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 7,8,14 and 15 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	J. EXP. MED. (1995), 181(3), 943-52 CODEN: JEMEAV;ISSN: 0022-1007, 1995 ANDERTON, STEPHEN M. ET AL 'Activation of T cells recognizing self 60-kD heat shock protein can protect against experimental arthritis' see abstract see page 944, left column, paragraph 2 see page 944, left column, paragraph 5 see page 945, left column, last paragraph - page 946, left column, paragraph 2 see page 946, left column, paragraph 3 - page 947, left column, paragraph 1	1,2,4-8, 11-15
E	WO,A,95 25744 (RIJKSUNIVERSITEIT UTRECHT) 28 September 1995 see page 4, line 33 - line 36 see page 7, line 6 - line 19 see page 8, line 11 - line 15 see page 9, line 14 - line 20 see page 11, line 15 - line 25 see page 18, line 18 - line 29 see tables I, II	1,2,4, 6-8, 10-15

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 95/02295

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/35 A61K39/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,90 10449 (COHEN, IRUN, R. ET AL.) 20 September 1990 see page 1, line 21 - page 2, line 3 see page 9, line 5 - line 22; examples 1,10,11 see page 66, line 11 - line 17 ---	1,4,6-8, 10,12-15
A	WO,A,92 04049 (RIJKSUNIVERSITEIT TE UTRECHT) 19 March 1992 cited in the application see page 7, line 5 - line 14 see page 8, line 10 - line 15 --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 December 1995	16. 01. 96

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)